Cardiotoxicity of Immune Checkpoint Inhibitors: a Systematic Review and Meta-Analysis of Randomized Clinical Trials

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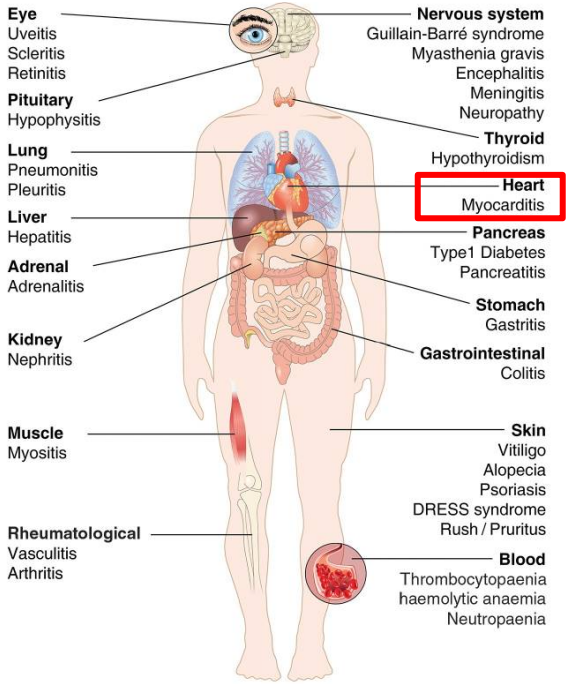
Disclosures

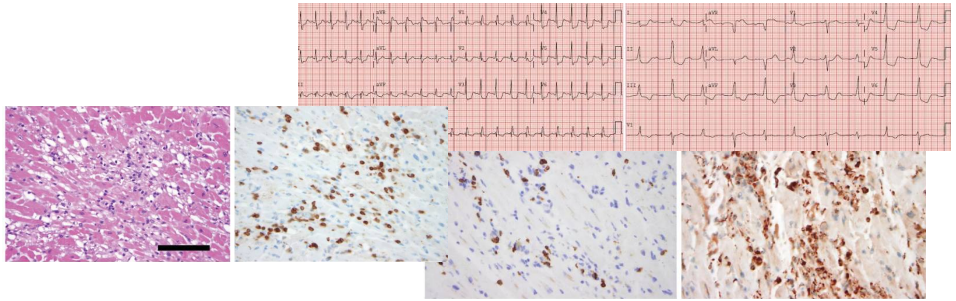
- I have no disclosures to declare.

Background

- **Immune checkpoint inhibitors (ICI)** have dramatically **improved the outcomes of patients with several cancers**
- Treatment related adverse events (AEs) induced by ICI are mostly **immune-related AEs** which can affect any organ, including the **cardiovascular system**



- The WHO database shows that the **mortality associated with ICI-related myocarditis** ranges **from 36% to 67%**



- Although there is increasing awareness of **cardiotoxicity induced by ICI**, its incidence in the most recent data has **not been systematically analyzed**

→ This provide us the rational to do a systematic review and meta-analysis aimed to assess the cardiac toxicity associated with ICI

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Varicchi et al., ESMO Open 2017
Johnson DB et al., NEJM 2016

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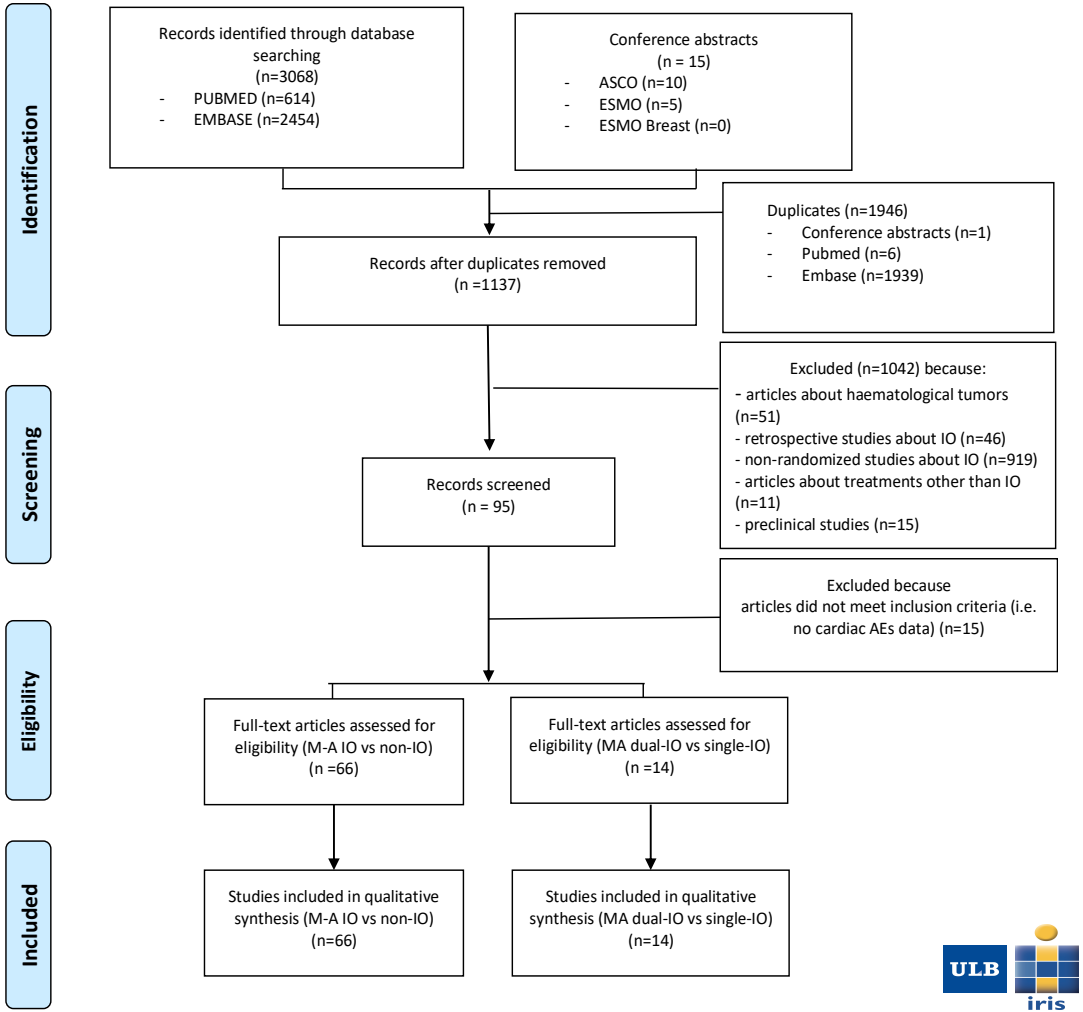
Methods: Objectives, Search strategy and data extraction

- **Systematic review and meta-analysis** conducted according to **PRISMA guidelines** and registered in **PROSPERO database** (ID: CRD42020183524)
- The **primary objective** was to compare the risk of cardiotoxicity induced by ICI with the risk of cardiotoxicity induced by different cancer treatments (non-ICI)
- The **secondary objective** was to compare the risk of cardiotoxicity induced by dual-agent ICI (immunotherapy combinations) with the risk of cardiotoxicity induced by single-agent ICI
- Systematic search of PubMed, MEDLINE, Embase databases, and conference proceedings up to June 30, 2020
- Inclusion of **all randomized clinical trials** comparing ICI with other treatments (primary objective) or dual-agent ICI vs single-agent ICI (secondary objective), in any solid tumor
- **Subgroup analyses** were performed to evaluate the impact of tumor type, setting of disease, line of treatment, and type of treatment

Liberati A et al., PRISMA statement for systematic reviews and meta-analysis, PLoS Med 2009
PROSPERO Database available at: https://www.crd.york.ac.uk/prospero/

Study Results

- **80 studies** including **35,337 pts** were included in the final analysis
  - **66 studies** with 34,664 pts for the primary objective
  - **14 studies** with 673 pts for the secondary objective



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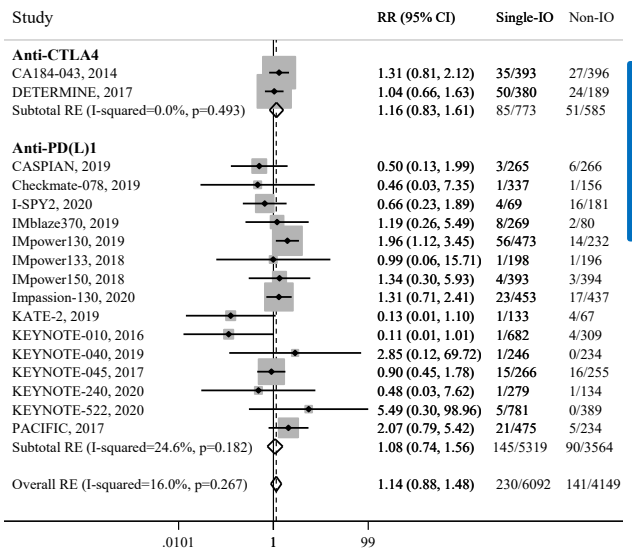
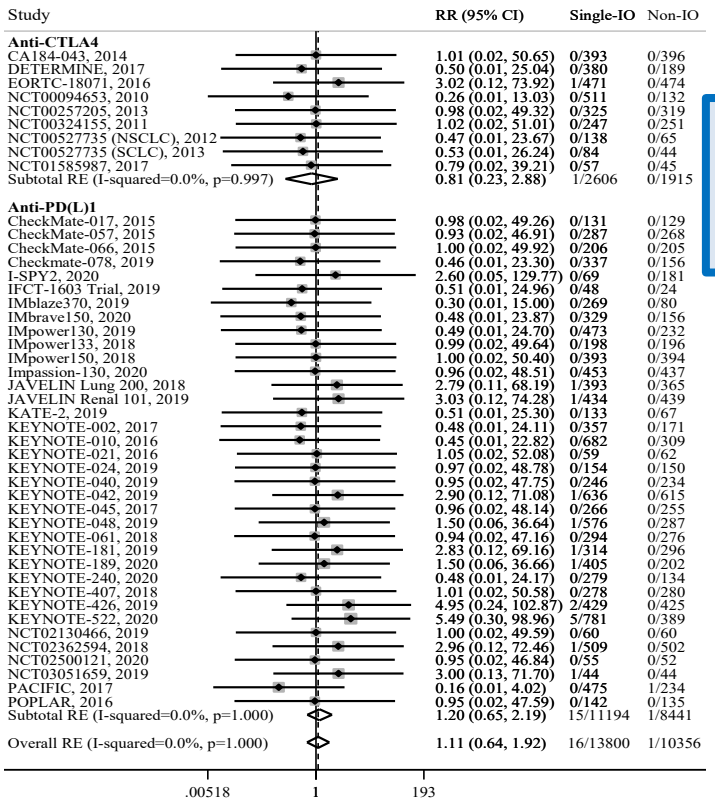
Primary Objective: ICI vs. Non-ICI treatments

No significant differences in terms of cardiac AEs (any) between ICI and non-ICI groups



RR 1.14, 95%CI 0.88-1.48, p=0.326 (I^2=16%)

No significant differences in terms of myocarditis risk between ICI and non-ICI groups



RR 1.11, 95%CI 0.64-1.92, p=0.701 (I^2=0%)

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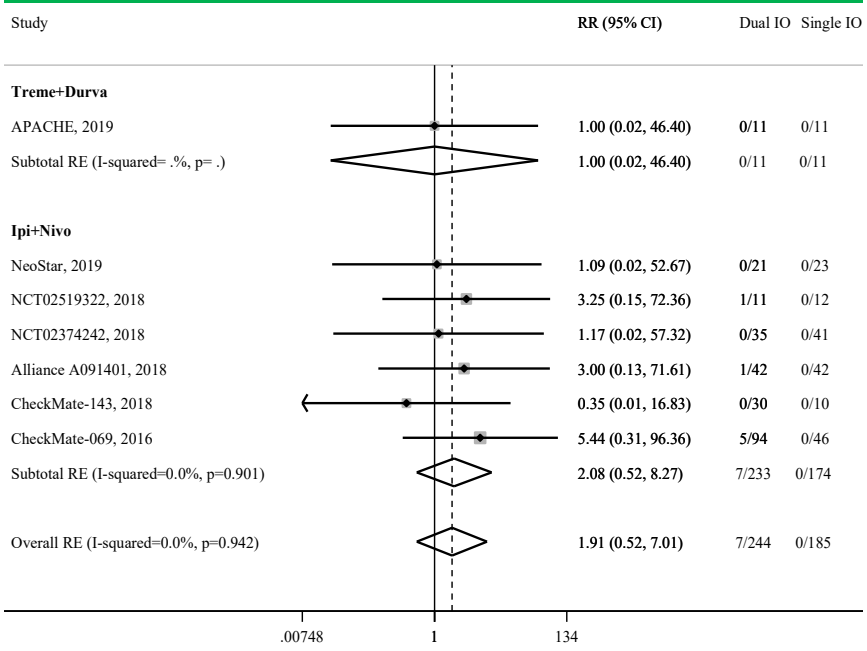
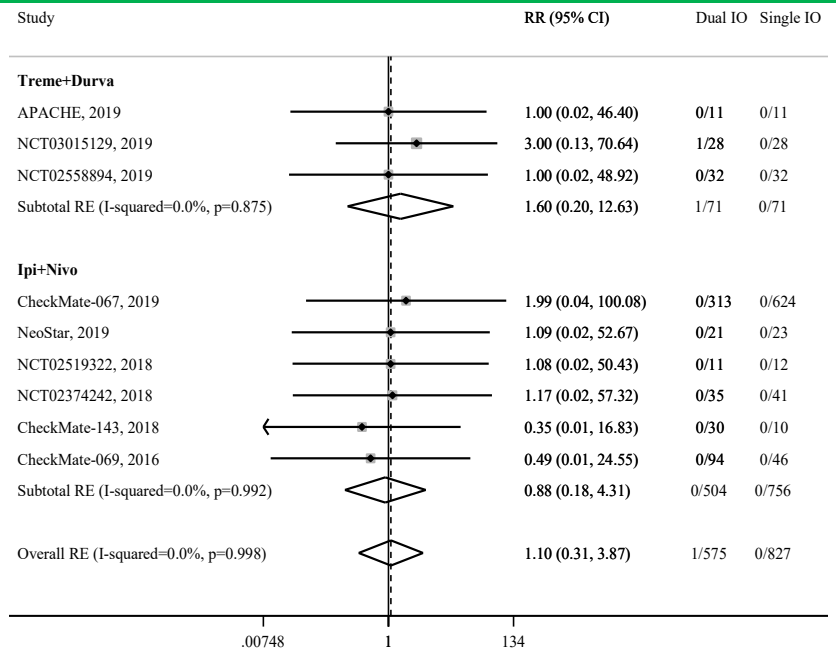
Secondary Objective: Dual ICI vs. Single ICI treatments

No significant differences in terms of cardiac AEs (any) between Dual ICI and Single ICI groups



RR 1.91, 95%CI 0.52-7.01, p=0.329, I^2=0%

No significant differences in terms of myocarditis risk between Dual ICI and Single ICI groups



RR 1.10, 95%CI 0.31-3.87, p=0.881, I^2=0%

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Pooled Incidences of Cardiac AEs

	ICI vs non-ICI groups			Dual ICI vs Single ICI groups		
	ICI-group events/N (%)	Non-ICI group events/N (%)	RR (95% CI)	Dual ICI events/N (%)	Single ICI events/N (%)	RR (95% CI)
Any cardiac AEs	230/6092 (3.78)	141/4149 (3.40)	1.14 (0.88-1.48), p=0.326	7/244 (2.87)	1/248 (0.40)	1.91 (0.52-7.01), p=0.329
Myocarditis	16/13800 (0.12)	1/10356 (0.01)	1.11 (0.64-1.92), p=0.701	2/1151 (0.17)	0	1.10 (0.31-3.87), p=0.881
Myocardial infarction	27/6607 (0.41)	12/4477 (0.27)	1.19 (0.63-2.23), p=0.596	1/202 (0.50)	0	0.98 (0.21-4.47), p=0.978
Pericarditis	31/6113 (0.51)	9/4162 (0.22)	1.14 (0.62-2.10), p=0.668	0	1/206 (0.49)	0.67 (0.16-2.76), p=0.580
Arrhytmias	104/5826 (1.79)	58/3894 (1.49)	1.32 (0.94-1.84), p=0.108	5/202 (2.48)	0	1.65 (0.40-6.89), p=0.491
Heart failure	28/6548 (0.43)	28/4415 (0.63)	0.61 (0.35-1.07), p=0.087	1/263 (0.38)	0	1.04 (0.25-4.26), p=0.962
Valvular disease	0	1/3894 (0.03)	0.63 (0.24-1.64), p=0.340	0	0	0.79 (0.16-3.83), p=0.770
Cardiac arrest	19/7854 (0.24)	5/5399 (0.09)	1.23 (0.61-2.47), p=0.558	0	0	0.79 (0.16-3.83), p=0.770
Cardiac death	55/16620 (0.33)	27/12987 (0.21)	1.07 (0.72-1.59), p=0.751	4/1458 (0.27)	0	1.28 (0.48-3.42), p=0.623

Conclusions (1)

- In our meta-analysis of randomized clinical trials, immunotherapy was **not associated with a higher risk of cardiotoxicity** compared to non-immunotherapy treatments.

- Moreover, immunotherapy combinations were not associated with a higher risk of cardiotoxicity compared to ICI in monotherapy

- Our study is the **largest meta-analysis** published thus far **about cardiotoxicity induced by ICI**, and we investigated not only myocarditis events, but also a **broader range of cardiac AEs,** including myocardial infarction, pericarditis, hearth failure, arrhythmias, valvular disease, cardiac arrest and cardiac death

Conclusions (2)

- Nonetheless, **not all studies** included in the meta-analysis **provided complete data about cardiac AEs**. Several studies presented only AEs occurring above a specified incidence, which might have ranged from 1% to 20%. This could favour **underreporting of rare AEs**, like cardiac events, and could mask the real incidence of this toxicity

- Despite the apparent cardiac safety of ICI, an effort for **comprehensive AEs reporting upon ICI clinical trials** publication, **regardless of AEs rarity**, should be pursued, in order to further investigate the incidence, treatment and outcomes of these rare but potentially fatal toxicities.

Ackowledgements

- *Cardiotoxicity of ICI m-a team:* Elisa Agostinetto, Daniel Eiger, Matteo Lambertini, Marcello Ceppi, Marco Bruzzone, Noam Pondè, Chris Plummer, Ahmad Hussein Awada, Martine Piccart, Evandro de Azambuja

Thank you for your attention!

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